UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,807	07/06/2006	David Paul Humphreys	CELL-0307	6569

20306 7590 03/05/2008

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
03/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,807	HUMPHREYS ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *19-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to comply*.

DETAILED ACTION

1. The preliminary amendment filed 06 July 2006 has been entered in full.

Election/Restrictions

2. Applicant's election with traverse of the invention of Group I, claims 1-18 and 27-30 in the reply filed on 06 December 2007 is acknowledged. The traversal is on the grounds that the cited prior art of Humphreys et al (WO 99/15549, 4/1/1999, IDS reference 43 filed 10/10/2006) does not disclose the replacement of the cysteine of CH1 with another amino acid and hence, the examiner's reliance on Humphreys is misplaced. This has been fully considered but is not found persuasive. It is noted that the claims recite that both the interchain cysteine of CL and the interchain cysteine of CH1 have been replaced with another amino acid. Applicants' argument is curious in view of the examples as pointed to by the examiner. Specifically, Example 1 of Humphreys et al states "PCR mutagenesis was used to change the interchain cysteines of cKappa and CH1 to serines" (see pg. 12, lines 29-30). Thus, Humphreys et al do teach replacement of the interchain cysteine of CH1 with another amino acid. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features, meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. Hence, in view of the teachings of Humphreys et al (supra) there is no technical relationship left over the prior art among the claimed inventions involving one or more of the same or corresponding special technical features, leaving two or more dependent claims without a single general inventive concept.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 19-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 1-18 and 27-30 are under consideration.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 10 October 2006 has been fully considered by the examiner. A signed and initialed copy of the IDS is included with the instant Office Action.

Sequence Requirements

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. Claims 12 and 14 are drawn to sequences (i.e., SEQ ID numbers), however, the instant application does not contain a sequence listing. Applicant cooperation is requested in checking the entire disclosure to ensure that the application is in sequence compliance.

7. Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply (see attached).

8. APPLICANT IS GIVEN THE TIME ALLOTED IN THIS OFFICE ACTION WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period. Direct the response to the undersigned.

Specification

9. It is noted that this application appears to claim subject matter disclosed in prior Application No. PCT/GB04/02870, filed July 1, 2004. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question

whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-7, 10-11, 12-13, 15-18, 27-28 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Carter P. J. (WO 93/06217, 4/1/1993) as evidenced by Rodrigues et al (The Journal of Immunology, 151(12), 6954-6961, December 15, 1993, IDS reference 20 filed 10/10/06) and Bodmer et al (WO 89/01974, 3/9/1989).

Carter teaches Fab and Fab' fragments in which both of the cysteines of the heavy and light chains which form the inter-chain (heavy-light) disulfide bond are substituted with serine wherein the cysteines of the interchain disulfide bond are necessarily located at position 214 of the light chain and position 233 of the heavy chain as evidenced by Rodrigues et al (e.g., see pg. 6955 2nd col.), and wherein the Fab or Fab' may include a hinge region, a modified hinge having one cysteine (e.g., Cys-X-X,

where X is Ala, Arg, Asp or Pro) or more than one cysteinyl residue (e.g., CPPC), or a naturally occurring hinge region such as human IgG1 (necessarily comprises SEQ ID NO:1 as evidenced by Bodmer et al, see Fig. 1), and wherein the free cysteine thiol(s) may be attached to a diagnostic or therapeutic agent (i.e., effector molecule) (see entire document, particularly abstract, pp. 7-8, 11-12, 15-17, 19-20 and 26-27). Carter et al also teaches pharmaceutical compositions comprising the Fab or Fab' fragments (e.g., two or more) and a pharmaceutically acceptable carrier (see pp. 27-28).

Thus. Carter et al anticipate the claims as evidenced by Rodriguez et al and Bodmer et al.

12. Claims 1-18 and 27-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 43 filed 10/10/06) as evidenced by Rodrigues et al (The Journal of Immunology, 151(12), 6954-6961, December 15, 1993, IDS reference 20 filed 10/10/06).

Humphreys et al teach antibody fragments comprising a Fab or Fab' wherein the interchain cysteines of the cKappa and CH1 have been mutated to serines (see Example 1, pg. 12), which are necessarily located at position 214 of the light chain and position 233 of the heavy chain as evidenced by Rodrigues et al (e.g., see pg. 6955, 2nd col.) and Humphreys teaches various hinge peptides comprising one, or two or more cysteines for the attachment of effector molecules, including polyethyleneglycol (PEG) and wherein the hinge peptides of Humphreys comprise sequences identical to SEQ ID Nos:1-3 (e.g., see entire document, particularly Table II, pp. 3-6, 8-11 and Examples). Further, Humphreys teaches di-Fab' production and partial reduction to expose reactive thiols to which one, two, three or more effector molecules can be attached, which reads upon claims 8-9 (e.g., see pp. 9 and 24). Humphreys also teaches pharmaceutical compositions comprising the antibody fragments (e.g., mixture of two or more antibody Fab or Fab' fragments) and a pharmaceutically acceptable excipient, diluent or carrier (see pg. 11).

Thus, Humphreys anticipate the claims as evidenced by Rodriguez et al.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1-7, 10, 15-18 and 27-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7 and 10 of U.S. Patent No. 6,642,356 B1 in view of Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 42 filed 10/20/06).

Claims 7 and 10 of U.S. Patent No. 6,642,356 B1 are drawn to a Fab or Fab' fragment comprising one polypeptide chain that comprises the amino acid sequence of SEQ ID NO:1 (e.g., TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the Fab or Fab' fragment has one or more effector or reporter molecules attached to it. Claims 7 and 10 of U.S. Patent No. 6,642,356 B1 do not specifically teach wherein either the interchain cysteines of the CH1 and CL are substituted with serine and wherein the effector molecule is PEG, or pharmaceutical compositions comprising the Fab or Fab' fragment and a pharmaceutically acceptable carrier or excipient. These deficiencies are made up for in the teachings of Humphreys.

Humphreys have been described supra. Humphreys also teaches that covalent attachment of PEG to proteins increases serum residence reduces immunogenicity and decreases proteolysis *in vivo*.

The claims in the instant application are obvious variants of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a Fab or Fab' fragment comprising the hinge sequence of SEQ ID NO:1 (TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the interchain cysteines of the CH1 and CL are substituted with serine and the free cysteine thiols of SEQ ID NO:1 are attached to PEG molecules and pharmaceutical compositions comprising such and a pharmaceutically acceptable carrier or excipient for immunodiagnosis or immunotherapy.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce a Fab or Fab' fragment comprising the hinge sequence of SEQ ID NO:1 (TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the interchain cysteines of the C_H1 and CL are substituted with serine and the free cysteine thiols of SEQ ID NO:1 are attached to PEG molecules and pharmaceutical compositions comprising such and a pharmaceutically acceptable carrier or excipient for immunodiagnosis or immunotherapy in view of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 and Humphreys because Humphreys teach Fab and Fab' fragments in which the interchain cysteines of the C_H1 and CL are substituted with serine and the hinge sequence TCPPCPXYCPPCPA is used for the attachment of one or more PEG molecules, which increase serum permanence, reduce immunogenicity and decrease proteolysis *in vivo*. Therefore, one of ordinary skill in the art would have been motivated to modify the Fab or Fab' fragments of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 in which the interchain cysteines of the C_H1 and CL are substituted with serine and the attachment of the PEG molecules to the free thiols in the hinge peptide of SEQ ID NO:1 since PEGylation has the potential to increase residence time,

reduce immunogenicity and decrease proteolysis *in vivo*. Further, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modifications because Humphreys teaches that removal of the interchain disulfide bond does not affect stability (see pg. 12). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a Fab or Fab' fragment comprising the hinge sequence of SEQ ID NO:1 (TCPPCPXYCPPCPA), wherein X and Y are neutral aliphatic L-amino acid residues and wherein the interchain cysteines of the C_H1 and CL are substituted with serine and the free cysteine thiols of SEQ ID NO:1 are attached to PEG molecules and pharmaceutical compositions comprising such and a pharmaceutically acceptable carrier or excipient for immunodiagnosis or immunotherapy in view of claims 7 and 10 of U.S. Patent No. 6,642,356 B1 and Humphreys.

Claims 1-7, 10, 15-18 and 27-30 are directed to an invention not patentably distinct from claims 7 and 10 of commonly assigned U.S. Patent No. 6,642,356 B1. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 6,642,356 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Singh et al. Analytical Biochemistry, 304(2):147-156, May 15, 2002.

Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate free thiol groups that are available for labeling.

16. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643